REMARKS

Claims 31-61 are pending in the application; claims 31-42 and 46-59 were withdrawn as directed to a nonelected invention. Applicants reserve the right to pursue these withdrawn claims in this or a related application.

Claims 43-45, 60, and 61 are under examination. Claims 43-45, 60, and 61 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and written description. Claims 43-45, 60, and 61 were rejected under 35 U.S.C. § 112, second paragraph. Claims 43-45 and 60 were rejected under 35 U.S.C. § 102.

Each of the rejections raised in the Office Action is addressed as follows.

Amendments

Applicants add new claim 62. Support for this claim is found in the claims as filed and in the specification, for example, in Example 7. Applicants, on page 31, line 3, amended the specification to refer to Figure 9, not Figure 8, which is clear from both the passage and the contents of the figure. No new matter has been added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

Claims 43-45, 60, and 61 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. For the following reasons, this rejection should be withdrawn.

Applicants first note that the claims, as amended, are directed to a culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, where the cells express a positive embryonic marker which is CDMP-1 or a marker co-expressed and/or co-detectable with this marker.

Applicants also note that the Office Action does not question that the specification enables subject matter to precursor cells expressing the CDMP-1 marker. Rather, the rejection is based on the assertion that (1) "the specification fails to provide specific guidance with regard to isolation of cells using any of the markers, other than CDMP 1, in order to arrive at the claimed invention," and (2) "it would require undue experimentation for one of skill in the art to identify the particular cell population, as claimed, for any of the contemplated uses in the specification." To sustain this rejection, the Examiner must find that a person of ordinary skill in the art would not have known that the methods outlined in the specification—in combination with applicants' description of the positive CDMP-1 marker (and negative markers) and the knowledge of skilled workers in the art—would enable the isolation and identification of other positive embryogenic markers. As discussed below, this is not the situation for the present case.

Having access to applicants' newly disclosed markers, for example, CDMP-1 and FGFR3, one skilled in the art could find additional markers from precursor cell lines absent "undue experimentation," simply by following the teachings found in applicants' specification. On this point, the Office is referred to the case of *In re Wands* (858 F.2d

731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)), which sets forth the CAFC standard for enablement in the biotechnology arts.[1] *Wands* holds that an invention is enabled so long as the teaching of the specification provides the invention without undue experimentation. *Wands* states that:

> the test [for determining whether experimentation is undue] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (emphasis added).

Applying this standard to the present case, it is clear that applicants' specification satisfies the first test outlined by the CAFC in *Wands*. According to *Wands*, a considerable amount of experimentation is permissible, if it is merely routine. Looking to applicants' situation, any "experimentation" involved in identifying and characterizing a marker co-expressed and/or co-detectable with CDMP-1 is indeed straightforward, and is rendered so by applicants' discovery of the various markers disclosed in the specification, including CDMP-1.

As detailed in the specification, applicants have identified and characterized not only the CDMP-1 marker, but also several negative markers including FGFR3. Because applicants have defined these markers, there is no undue experimentation involved in

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[1] The Examiner supports the lack of enablement rejection by applying the *Wands* factors to be considered in determining whether practice of a claimed invention would require undue experimentation. In applying the *Wands* factors to the present facts, the Examiner has unjustifiably reinterpreted those factors to render them more stringent than the statute or the case law, including *Wands*, permits.

ascertaining additional markers within the scope of the present claims. For example, if one skilled in the art wished to identify and characterize additional markers, they would simply use applicants' disclosed methods for identifying precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, where the cells express the positive embryogenic marker CDMP-1, and identify additional markers which are co-expressed and/or co-detectable with CDMP-1.

Identification of such markers involves routine experimentation delineated in applicants' specification. The same methods used to identify the CDMP-1 marker. Accordingly, there is no basis for concluding that one skilled in the art, equipped with applicants' positive CDMP-1 embryonic marker and standard methods known in the art, would not be able to identify additional markers which fall within the scope of the claims.

Alternatively, applying the second test of *Wands*, a "reasonable amount of guidance" is also provided by applicants' teaching. Applicants, in their specification, outline general methods useful for identifying and characterizing additional positive embryogenic markers (see, for example, Examples 1-3), and also provide methods for testing the phenotypic stability of such cells (Examples 4 and 5), as well as examining the ability of such cells to form cartilage in vitro and in vivo (Examples 7 and 8, respectively). Such teachings for identifying expressed positive markers are, in and of themselves, more than adequate to satisfy the requisite "reasonable amount of guidance." Applicants assert therefore that this general teaching easily places their specification within the bounds set out by *Wands* in its second test for enablement.

In sum, armed with applicants' teachings and disclosed positive embryogenic markers, it would be a trivial matter to identify additional markers from the precursor cells isolated and characterized by applicants using the methods outlined in their specification. Any "experimentation" involved would be entirely straightforward and routine. In essence, applicants' situation is indistinguishable from the facts in *Wands* where the Federal Circuit reversed the Examiner, concluding that the process of screening hybridomas to select those having the desired property was straightforward with a very high likelihood of success. As discussed above, applicants' specification satisfies the enablement standard under, not one, but both of the alternative tests set forth by *Wands*. If the Examiner disagrees with this analysis, applicants request that the Office provide bases for why applicants' specification would fail to identify other positive embryogenic markers falling within the scope of applicants' present claims. Such an evaluation will clearly establish that the claims are enabled under current standards for § 112, first paragraph.

The specification adequately describes the methods to be used to practice the invention. Applicants know of no information a practitioner would require to carry out the invention that is not described in detail in the application. Applicants note that the type of guidance pointed out above is sufficient to satisfy this *Wands* factor.

Moreover, on this issue, applicants note that no evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in applicants' specification regarding enablement with respect to identifying "a marker co-

expressed and/or co-detectable with CDMP-1." As stated in *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

On this basis, as well, the facts in the present case compel withdrawal of the § 112, ¶ 1 enablement rejection, and applicants request reconsideration on this issue.

In addition, applicants note that claim 61 and new claim 62, which is directed to the negative marker FGFR3, are clearly free of the enablement rejection. Applicants' specification, for example, at page 31 (ll. 8 -- 19) states (emphasis added):

> It can be seen that CDMP1 is downregulated as skeletal precursor cells enter chondrogenesis and mature to chondrocyte phenotype. The mature chondocyte phenotype is by the appearance of type 11 collagen, type X collagen, FGFR3 (fibroblast growth factor 3) and BMP2. A positive marker in accordance with the present invention such as the CDMP-1 marker or a marker or factor co-expressed or co- detectable with this marker, and a negative marker such as the chondrocyte markers type 11 collagen, type X collagen, FGFR3 and BMP2 or a marker co-expressed or co- detectable with any or all of these markers, are mutually exclusive. The skeletal precursor cells of the present invention may be identified by a positive marker such as CDMP-1 (or a marker or factor which is co-expressed or co-detectable with CDMP-1) which is not expressed at the same time as a negative marker such as FGFR3 or [ ] another factor or marker co-expressed or with FGFR3.

Clearly, applicants' demonstrated that FGFR3 is a negative marker, and that markers such as type 11 collagen, type X collagen, and BMP2 represent markers co-expressed or

co-detectable with FGFR3. Claim 61 and new claim 62 are clearly enabled by the present specification.

Applicants also note that there is no requirement that the specification contain proof of therapeutic benefit, as is seemingly required here. Applicants note that human testing is not required, for enablement purposes, to support claims of an *in vivo* utility of a biomedical invention. The Federal Circuit has repeatedly stated (*Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994), affirming *In re Watson*, 517 F.2d 465, 476 (C.C.P.A. 1975) and *In re Sichert*, 566 F.2d 1154, 1160 (C.C.P.A. 1977)):

> Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings ... Congress has given the responsibility to the FDA, not to the [PTO].

The Federal Circuit, in reversing a Board of Patent Appeals and Interferences decision that in vitro data did not support in vivo applications, stated (*In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995)):

> The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

Accordingly, evidence from sources other than human efficacy trials is acceptable when patenting compositions useful for treating human disease. Indeed, the law is very clear on the interpretation of the enablement requirement. The first paragraph of § 112 "requires nothing more than objective enablement" and, in a case in which the Patent Office questions the enablement of a claim, evidence from sources other than human efficacy trials is acceptable.

Applicants' specification meets this standard. Applicants' specification teaches (1) formation of cartilage in vitro (Example 6) and (2) the enhancement of the cartilage forming ability of chondrocytes with skeletal precursors both in vitro and in vivo (Example 7). Indeed, applicants note on page 29 (lines 32-34) states:

> The addition of human skeletal precursor cells from example 3 to pig articular chondrocytes resulted in a dramatic impact on the cartilage forming potential of the chondrocytic cells. In particular, an increase in the amount of cartilage made and at the same time a decrease in the threshold of the in vivo assay (i. e. less than one million cells were required for cartilage formation and organization) were observed.

Thus, applicants' results provide an expectation that the claimed method will be successful and demonstrates that the specification fully enables the claimed invention.

To dismiss the findings of applicants as non-predictive because "it is well known in the art that, upon injection of cells that are not autologous to the individual, could fail to integrate into the host, and function in an appropriate fashion" without specific evidence is entirely inappropriate. Models of the sort described in applicants' specification have been used extensively. Moreover, the Office's reliance on Hui is inappropriate because applicants in fact identified several markers of useful in identifying skeletal precursors; a goal Hui proclaims as desirable. Furthermore, the Examiner's concerns regarding autologous cell transplantation are unwarranted. As noted in applicants' specification, despite its drawbacks, "autologous chondrocyte transplantation is becoming a widely accepted technique for repair of joint surface defects." Specification page 10 (ll. 10-12).

In addition, the Office has provided no evidence that the immunodeficent mouse model is unreliable or inappropriate for testing potential human therapies in this particular case. Accordingly, in this respect, applicants respectfully submit that, at the time of application filing, a skilled artisan, practicing no more than routine experimentation, could have generated the claimed precursor cells used in the present invention. These cells, when transplanted into a patient, form replacement skeletal or connective tissue in critical locations and adopt the appropriate phenotype necessary to correct the repair a deficiency, as disclosed in the specification. For these foregoing reasons too, applicants submit that the specification fully enables the practice of the claimed invention and this rejection on this basis should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description

Claims 43-45, 60, and 61 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. For the following reasons, this rejection should be withdrawn.

The statute sets the standard for measuring sufficiency of disclosure: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same." 35 U.S.C. § 112, ¶ 1. In written description cases, "[t]he primary consideration is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art

by the disclosure." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976) (emphasis added). The written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citations omitted). Thus, § 112, ¶ 1 ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicants' specification plainly meets this standard at the time the application was filed.

In this case, the application teaches one of ordinary skill production of a "culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway." The application also teaches cells that express a positive embryonic marker which is CDMP-1 or a marker co-expressed and/or co-detectable with this marker CDMP-1.

For example, the written description supporting a single claim -- claim 43 -- follows:

Claim limitation	**Exemplary support in the '994 application**
A culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a	A first object of the present invention is the identification and characterization of skeletal precursor cells in a wide range of easily accessible and **expandable** sources; Examples 1 and 2;

post-natal skeletal differentiation pathway leading to skeletal or connective tissue	The present invention relates to the use of embryonic markers which identify that certain precursor cells have entered a **post-natal differentiation pathway**. The present invention is particularly useful with respect to mammalian precursor cells, in particular, skeletal precursor cells, more in particular **skeletal** precursor cells of humans and horses, but is not limited thereto. The present invention makes use of embryonic markers ... Such embryonic markers are considered to be a necessary part of or to be associated with a necessary part of embryogenesis as the growing organism during differentiation has also the necessity of identifying differentiated or partly differentiated cells and this must be achieved biochemically. Hence, the present invention has wide application; and The present invention relates to the field of tissue engineering in and more specifically to the identification of skeletal precursor cell populations for the repair of **connective tissues, including skeletal tissues in vivo**.
wherein the cells express a positive embryonic marker which is CDMP-1	[T]he present invention is [directed to the] use a set of markers. These markers may be either **positive markers** ... or negative markers. Absence of a negative marker can be used as a positive marker. (p. 12, ll. 4-6) The method to be followed is to identify the **embryonic marker** or markers that identify precursor cells for the specific tissue cells to be repaired, and then to select cells from the organism which exhibit the marker.
or a marker co-expressed and/or co-detectable with this marker.	With respect to **co-expression**, in the context of the present invention, is meant that a factor is expressed whenever another factor or marker is expressed in or on a cell. For instance, where a morphogenic protein is used as a marker, and more in particular the cartilage-derived morphogenic protein CDMP-1 or a thereof are/is expressed, co-expression requires that a co-expressed marker is only present or expressed when the morphogenic marker is expressed. Hence, the factor is linked with the same specific post-natal differentiation pathway as the morphogenic protein it co-expresses with, such as CDMP-1. It preferentially is upregulated/downregulated together with

	the marker. It will for instance when the precursor cells undergo differentiation such as towards the chondrocytic phenotype. Such co-expressing marker further is preferably expressed at detectable levels. Such co-expressed factor can be a recognizable cell surface marker, detectable via polyclonal or monoclonal antibodies and/or specific ligands. The co-expressed factor may also include any functional or structural of CDMP-1. (p. 13, ll. 17-31)

Applicants also note that claim 61, as well as new claim 62 are clearly described in applicants' specification. For example, applicants' specification at page 17 (ll. 27) – page 18 (ll. 5) teaches:

> A first embodiment of the present invention consists of the use of cartilage-derived morphogenetic protein CDMP-1 or a transforming growth factor having at least 80% with CDMP-1 as a positive marker of skeletal precursor cells from any part of a mammalian body or use of a factor or marker which is co-expressed or is co- detectable with CDMP-1.... For instance, when skeletal precursor cells differentiate into chondrocytes, the expression of cartilage markers such as type 11 collagen, FGFR3, type IX collagen, or type XI collagen, is always preceded by the disappearance of CDMP-1. Markers such as FGFR3, type 11 collagen, type IX collagen, or type XI collagen or markers or factors co-expressed or with these markers are negative markers. Relevant gene products co-expressed with CDMP-1 or a CDMP-1 related gene can be used in accordance with the present invention to identify positively skeletal precursor cells within a reference population.

As evidenced by the cited sections of the specification, the language recited in the present claims is described in the application as filed. Applicants' specification describes what is claimed.

Applicants also note that it is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be

sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations. *In re Wertheim,* 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In this case, applicants' specification conveys clearly to those skilled in the art to whom it is addressed the information that they have invented the specific subject matter claimed. The written description basis for rejection should therefore be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 43-45, 60, and 61 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, with respect to independent claim 43, the Office asserts that the recitation of the phrase "differentiated, pluripotent precursor cell" is indefinite because

> It is unclear how a cell can be differentiated and pluripotent simultaneously, as a differentiated cell is one that is highly specialized (see pp. 13-14, of the specification). A pluripotent cell can give rise to a differentiated cell, but it is unclear how the pluripotent cell is also a differentiated cell.

One skilled in the art would readily understand the meaning of this phrase based on the specification. For example, on page 16 (lines 5-7), the specification, for example, teaches that some cells, such as a skeletal precursor cell is a "cell no longer undifferentiated, but already committed towards any of the differentiation pathways of the skeletal tissues (emphasis added). The cell is still pluripotent and may differentiate

into any of the connective tissues or a sub-group thereof." Given such description, applicants submit that the metes and bounds of the present claims are clearly defined and this basis of the indefiniteness rejection should be withdrawn.

In addition, claim 43 was deemed unclear in reciting "a marker co-expressed and/or co-detected with this [positive embryogenic] marker" because it encompasses markers that are co-expressed but potentially not detectable with a particular marker. Again, the skilled artisan would readily understand the meaning of this phrase based on applicants' specification. For example, relevant gene products co-expressed with a marker may be monitored (page 18, lines 3-5) or cell surface markers, co-detectable with a positive embyrogenic marker, may be monitored (page 18, lines 32-35). This basis of the indefiniteness rejection should also be withdrawn.

Finally, in view of the foregoing remarks, the rejection of claims 44, 45, and 61 should also be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 43-45 and 60 were rejected under 35 U.S.C. § 102 as anticipated by Connolly (WO 98/35022). For the following reasons, this rejection is respectfully traversed.

A prior art reference anticipates a patent claim only if the reference discloses, either expressly or inherently, all of the limitations of the claim (*Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)).

The Office acknowledges, as is appropriate, that Connolly does not expressly disclose a culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue.

In rejecting claims 43-45 and 60 over Connolly, the Office relies instead entirely on inherency, stating:

> Connolly teach methods of identifying human mesenchymal stem cells using the expression of p21 cyclin inhibitor protein ($p21^{CIP1}$) (see Abstract). Particularly, they teach that $p21^{CIP1}$ is found to be implicated as an effector of the TGFβ signaling pathway (see p. 3, 1st paragraph). They further teach that the isolated cells can be used in methods for producing pharmaceuticals, and for methods of tissue repair, and further as *in vivo* implants for transplantation. See p. 4. Accordingly, because Connolly teach the isolation of cells that express a marker encompassed by the claims, they anticipate the claimed invention. Further, because the cells express a particular marker encompassed by the claims, they would inherently be cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue. (Office Action, pages 10-11, emphasis added).

Applicants respectfully disagree.

As an initial matter, applicants note that Connolly fails to teach precursor cells that express a positive embryonic marker which is CDMP-1 or a marker co-expressed and/or co-detectable with CDMP-1. Absent such teaching, Connolly fails to anticipate the claims as amended.

Connolly also fails to disclose a "a culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue" (claim 43) or "a

therapeutic composition comprising a culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue" (claim 44). In fact, Connolly never even discusses skeletal or connective tissue, let alone cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue.

On this basis too, the § 102 rejection of independent claims 43 and 44 should be withdrawn.

In addition, Connolly fails to inherently anticipate the claimed method because it fails to satisfy the strict "certainty" standard set out by the case law for inherent anticipation. As summarized in the Federal Circuit decision, *Finnigan Corp. v. ITC*, 51 U.S.P.Q.2d 1001, 1009 (Fed. Cir. 1999) (citing *Continental Can Co., USA v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991)) (emphasis added):

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is <u>necessarily</u> present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Oelrich,* 666 F.2d 578, 581, 212USPQ 323, 326 (CCPA 1981*)*(quoting *Hansgirg v. Kemmer,* 102 F.d 212, 214, 40 USPQ 665, 667 (CCPA 1939)) [states]:
>
> <u>Inherency</u>, however <u>may not be established by probabilities or possibilities</u>. The mere fact that a certain thing <u>may</u> result from a given set of circumstances is not sufficient.

While the Office states that "because the cells express a particular marker encompassed

by the claims, they would inherently be cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue," the Office has provided no evidence supporting its contention that the functionally defined limitation of the claimed culture of cells (claim 43) or the therapeutic composition (claim 44) are inherent characteristics of any teaching found in the Connolly reference. The mere possibility that Connolly's description on page 3, 1st paragraph might be understood by one of skill in the art to disclose a culture of isolated and expanded viable, differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue is insufficient to show that it is inherently disclosed in the reference. Because one skilled in the art would not necessarily recognize that cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue is in fact disclosed in the Connolly reference, it is not clear and convincing that the Connolly reference inherently anticipates either claim 43 or claim 44. Connolly does not satisfy the standard for inherency. As stated above by the Federal Circuit, "inherency…may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

For all of the above reasons, the inherency rejection of claim 43-45 should be withdrawn.

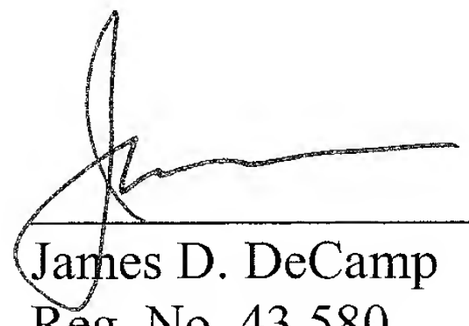
CONCLUSION

Applicants submit that the application is in condition for allowance, and this action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 21 April 2006



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